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ADVANCES IN DISSOLUTION TECHNOLOGY: DESIGN, PROS AND CONS

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ABSTRACT

To date dissolution tests are considered to be the most reliable predictors of bioavailability of drugs. Dissolution tests are critical and difficult to carry out properly. A review of different dissolution apparatii currently in use or employed in the past is present along with the advantages and disadvantages offered by each. Criteria as to design, operation, sensitivity, etc. of an in vitro dissolution system are outlined which would assist in fabrication of a more efficient and reliable apparatus. If one is to obtain meaningful results, care and attention must be given to those aspects that have been identified as crucial. To date no universal dissolutiuon test has yet been devised that in every instance gives the same rank order for in vitro dissolution and in vivo availability for different formulation and batches.

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INTRODUCTION

The liberation of an active agent from a dosage form, its physiological availability and its ultimate therapeutic effect, govern the efficacy of the dosage form in question. Effective *in vitro* dissolution studies have more than often been considered as the stepping stones towards the fabrication of a therapeutically effective drug delivery system. Since long investigators have been confronted with the question as to "the" *in vitro* dissolution system closely mimicing the environment offered by a biological system. In this pursuit numerous and diversified attempts have been made to develop such a system giving comparable results both *in vitro* and *in vivo*. It has been recognized that the dissolution rate of a drug from its dosage form can become the rate limiting process in its physiological availability. The technological development of the various dissolution systems and their construction along with their major advantages and disadvantages is the subject of this report.

Literature to-date reveals an array of dissolution systems used in the monitoring of drug released from a dosage form (1-16). Table I enlists the different dissolution systems currently in use or employed in the past. It should be noted at the outset that dissolution systems which are minor modifications of the ones listed are excluded from Table I. These systems can be characterized according to their status *viz*, official or unofficial. Of the many dissolution apparatii that have been proposed for *in-vitro* release of medicament from solid dosage forms, FDA concentrates on three; the USP Rotating Basket Apparatus, the USP Paddle

TABLE I

CLASSIFICATION OF IN VITRO DISSOLUTION APPARATII ACCORDING TO THEIR STATUS (OFFICIAL/UNOFFICIAL)

IN VITRO DISSOLUTION SYSTEM	STATUS	REFERENCE NUMBER
Tumbling Method	Unofficial	1
Beaker Method	Unofficial	2
Rotating Disc Method	Unofficial	26-29
USP Rotating Basket	Official	11, 30
Modified USP Basket	Unofficial	33
USP Paddle Apparatus	Official	30
Rotating Filter-Stationary Basket	Unofficial	34, 35
Magnetic Basket Apparatus	Unofficial	37
Continuous Flow Apparatus by		
Pernarowski, et al.	Unofficial	12
Baum and Walker	Unofficial	13
Tingstad and Riegelman	Unofficial	14
Cakiryildiz, et al.	Unofficial	51
Pressure Controlled Apparatus	Unofficial	52

Apparatus, and the Rotating Filter-Stationary Basket Apparatus (1). Furthermore, these in vitro dissolution systems can also be classified in accordance with the operating conditions they offer viz., natural convection non-sink, forced convection non-sink, and forced convection sink conditions as shown in Table II. Unquestionably, it must be noted that some dissolution systems can be

TABLE II

CLASSIFICATION OF IN VITRO DISSOLUTION SYSTEMS ACCORDING TO THE CONDITIONS OFFERED

FORCED CONVECTION NON-SINK METHODS:

- Tumbling Method (1930) + Beaker Method (1961)
- Rotating Disc Method (1962)
- USP Rotating Basket (1969)
- Magnetic Basket Apparatus (1972)
- Modified USP Basket (1973) + Rotating Filter Stationary Basket (1974)
- USP Paddle Apparatus (1978)

FORCED CONVECTION SINK METHOD*

- Continuous Flow Apparatii
  - Pernarowski, et al., (1968)
  - Baum and Walker (1969)
  - Tingstad and Riegelman (1970)
  - Cakiryildiz, et al., (1975)
- Pressure Controlled Apparatus (1979)

*In addition to the ones listed, apparatii enlisted under "Forced Convection Non-Sink Methods" marked with (+) could be included in this category with minor modifications.

categorized in more than one class. The forthcoming sections of the text will be devoted to brief discussion of each system, as to its design, offered advantages and disadvantages, as enumerated in Table I.

Tumbling Method:

Wruble (1), as early as 1930 employed test tubes containing the dosage form (tablet) in the dissolution medium clamped to a revolving drum rotated a 6 to 12 r.p.m. in a water bath at 37°C. The tubes were removed at various time intervals and the solution assayed for drug content (Fig. 1). Sonder and Ellenbogen (17), used a similar procedure in which 90 ml bottles containing the tablet in 60 ml dissolution medium were rotated at 40 r.p.m. at 37°C. A similar technique was used by Higuchi (18, 19) where the rotation was maintained at 6 r.p.m.

Levy Method or Beaker Method:

Levy and Hayes (2) applied to tablet the apparatus first used by Parrott et al., (20) for the determination of dissolution rate of pure benzoic acid spheres. The dissolution assembly consists of a 400 ml beaker immersed in a constant terature bath adjusted to 37 ± 0.1°C. A three blade, 5 cm diameter polyethylene stirrer is accurately centered and rotated at 59 r.p.m. (Fig. 2). The tablet is gently dropped down the side of the beaker and samples of the solution withdrawn for analysis. The dimensions of the beaker, stirrer and immersion are carefully controlled so that the solution quickly equilibrates without disturbing the tablet which upon disintegration covers an area of 1-2 cm^2 at the base of the beaker. This method has been adopted by various investigators (21, 22, 23) for intrinsic dissolution rate. Sheffer and Higuchi (24) employed an Erlenmeyer

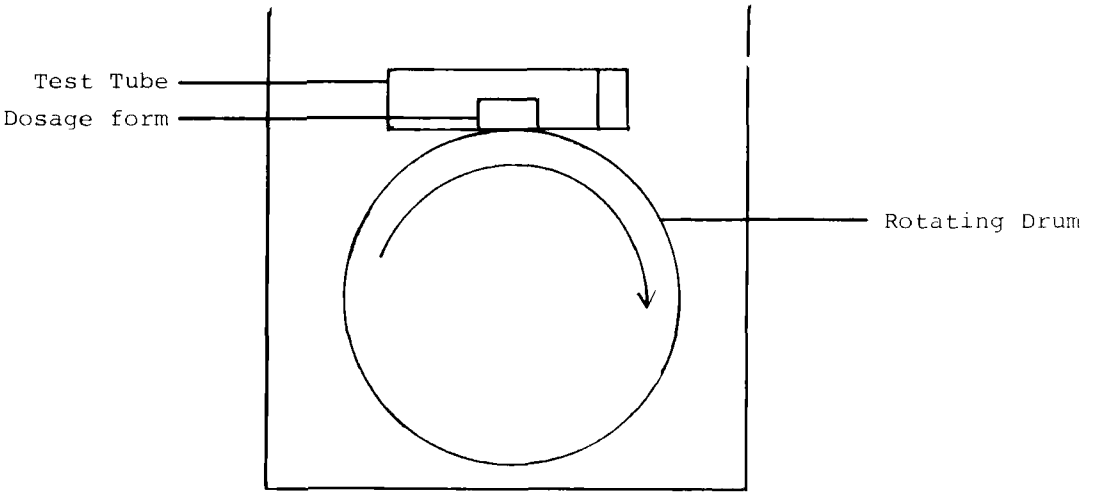

FIGURE 1 : Schematic Diagram of Wruble Apparatus (Tumbling Method).

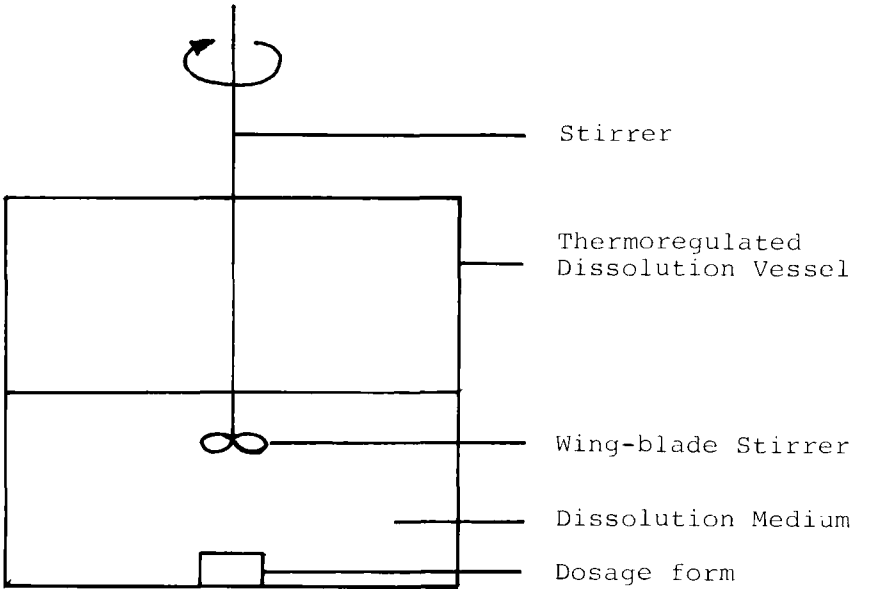

FIGURE 2 : Schematic Diagram of Levy Apparatus (Beaker Metnod).

flask and a magnetic stirrer. Broadbent, Mitchell and O'Reilly (25) used a shaker for stirring and Edmundson and Lees (6) have determined dissolution by measuring particle size.

The inherent simplicity in the design of the apparatus and the ease of control of experimental conditions provide for its wide applicability in the determination of dissolution rates. However, this system does not lend itself for characterization of intrinsic dissolution rates of dosage forms per se.

Rotating Disc Method:

One of the more accurate methodologies used earlier, to determine the intrinsic dissolution rate of a solid dosage form is the Rotating Disc Method. Levy and Sahli (26) have described the use of plexiglass holders that expose a single surface of the tablet to the dissolution medium. The studies of variation in intrinsic dissolution rate with media, temperature, etc., are most conveniently performed from surfaces whose areas remain constant (27).

Flat-faced, one-half inch diameter tablets of pure drug were prepared by means of a specially modified hydraulic press and mounted on plexiglass holders. The holder is attached to a metal shaft whose stirring speed is controlled precisely. The plexiglass holder is immersed in 500 ml of dissolution medium maintained at 37 ± 1^{o} C. The holder is immersed into a depth of 1 inch in the dissolution medium and rotated at a speed of 555 r.p.m. (Fig. 3). The volume of the dissolution medium is kept constant and the tablet in the holder is weighed before and after the assay.

It is frequently desirable to measure dissolution rates of a given drug at different rates of agitation in order to fully characterize its dissolution behavior and to elucidate the mechanism

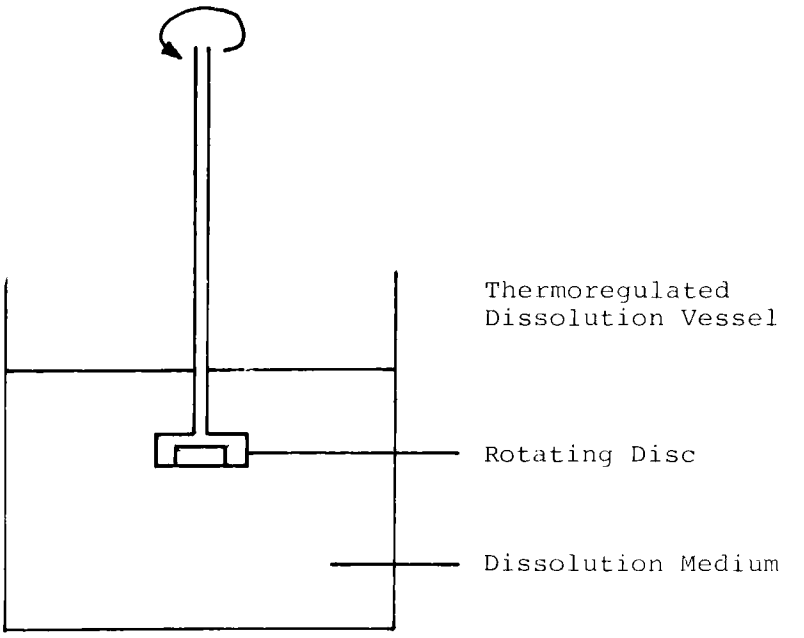

FIGURE 3 : Schematic Diagram of Rotating Disc Apparatus.

governing the rate of dissolution (28). Levy and Tanski (29) demonstrated with a special assembly the nonvariability in dissolution rate at low speeds of rotation. Dissolution rate experiments at speeds as low as 4 r.p.m. and of 6 hours duration can be carried out without measurable variation in rotational speed. This assembly offers precision speed control, wide range of rotation rates, shaft concentricity and constant speed over prolonged periods of time. This assembly is particularly useful for dissolution rate studies at very low rates of rotation. Furthermore, this apparatus is useful for the determination of intrinsic dissolution rates which may be insufficient in itself as regards to its multiple use in dissolution rate measurements.

USP Rotating Basket Apparatus:

Figure 4 illustrates the USP Rotating Basket Apparatus. USP lists the specifications of various parts used in its construction. The basket is centered within 2 mm of the centerline of the vessel. The rotating basket is made of # 10 mesh stainless steel approximately 2.2 cms in diameter and 2.8 cms high. A lid with a center porthole and other portholes is placed over the vessel. The rotation of the shaft is maintained at 100 r.p.m. The temperature of the medium is maintained at 37 ± 0.5^{o} C. In this aliquots should be withdrawn midway between the surface of the dissolution medium and the bottom of the vessel and midway between the cylindrical edge of the basket and the wall of the vessel. This specification was set up by the National Center for Drug Analysis in consideration of non-conformance of the specifications set by the USP. Modifications of this apparatus has been the subject of intensive study by the Joint USP-NF Panel on Physiological Availability and is designated as Method I in the compendia.

Cook, Chang, and Mainville (31) designed a stainless steel wire basket in a Lucite frame. The basket was cylindrical in shape, 2.5 cm in diameter and 6.5 cm long. The basket was positioned in a jar containing 2 liters of dissolution medium and stirred by a T-shaped glass stirrer rotated at 150 r.p.m. This apparatus was also studied by the Joint USP-NF Panel; however, due to a lack of reproducibility, this method was not considered further.

Basket wobble can be created by a wobbling shaft, a bent shaft or by the basket bottom being out of line with the top of the basket. The shaft or basket should be replaced if the wobbling is significant. Baskets with burrs of defects should not be used.

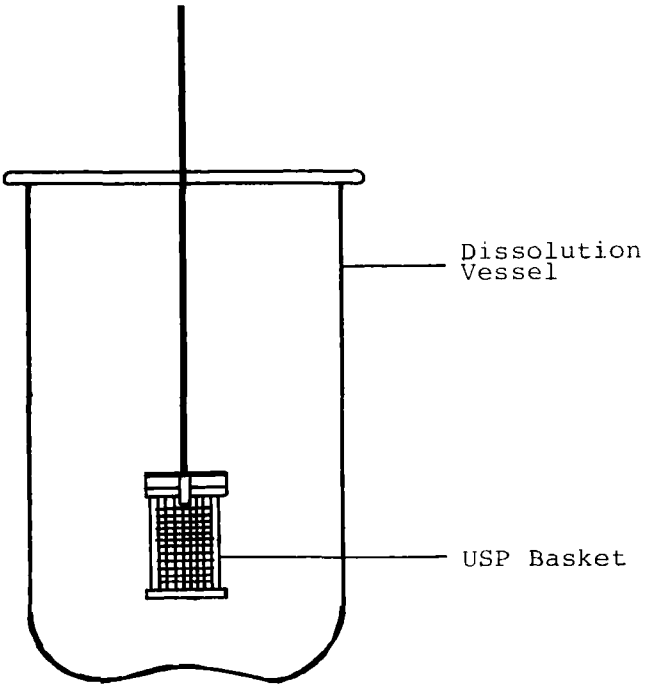

FIGURE 4 : Schematic Diagram of USP Rotating Basket Apparatus.

Each basket must be individually set to a position 2.5 cm from the bottom of its vessel and the vessel should be marked to reproduce the positioning of the basket.

USP specifies the use of six baskets at a time (32). Depending on the type of apparatus, either one basket is lowered in the specified dissolution medium at one time or all six baskets are lowered simultaneously. The basket should remain in motion while the analyst is withdrawing aliquots at specific intervals for the measurement of drug content till the end of the dissolution period. The sampling intervals are initiated from the time of lowering of the basket in the medium.

The location of the dosage form in the stainless steel woven basket should be noted immediately at the commencement of the test. Tablets should be at the bottom of the basket. Capsules should be near the top of the basket. Variability in the location of the dosage form in the basket in repetitive tests may lead to erroneous results. It has been observed, for instance, that a tablet may occasionally be suspended on an air bubble directly under the disk to which the basket is dipped. Results for such suspended tablets are usually considerably lower than the results for the tablets located at the bottom of the basket.

Modified USP Basket Apparatus:

The purpose of the basket in the USP-NF apparatus presumably is to hold the tablet or capsule in a fixed position during the disintegration process. In essence, the distance of the tablet from the center of rotation is fixed within small limits. Usually, disintegration of a tablet is involved during the dissolution test. The flow of solvent through the basket must be sufficient to disperse the tablet components and sweep them through the openings in the basket screen.

Consequently, a configurational change was introduced in the standard USP-NF Rotating Basket Apparatus. It has been reported to exhibit better flow of the solvent through the basket (33). The stainless steel stirring rod of the apparatus is bent at 90° angle just above the basket to yield an L-shaped configuration as shown in Fig. 5. This modification gave a maximum stirring radius of 6.1 cm for the tablet. Later for the tablet, a holder of teflon was designed (6). A cylinder of # 24 mesh stainless screen is seam welded to fit tightly over the teflon holder. This device ensures

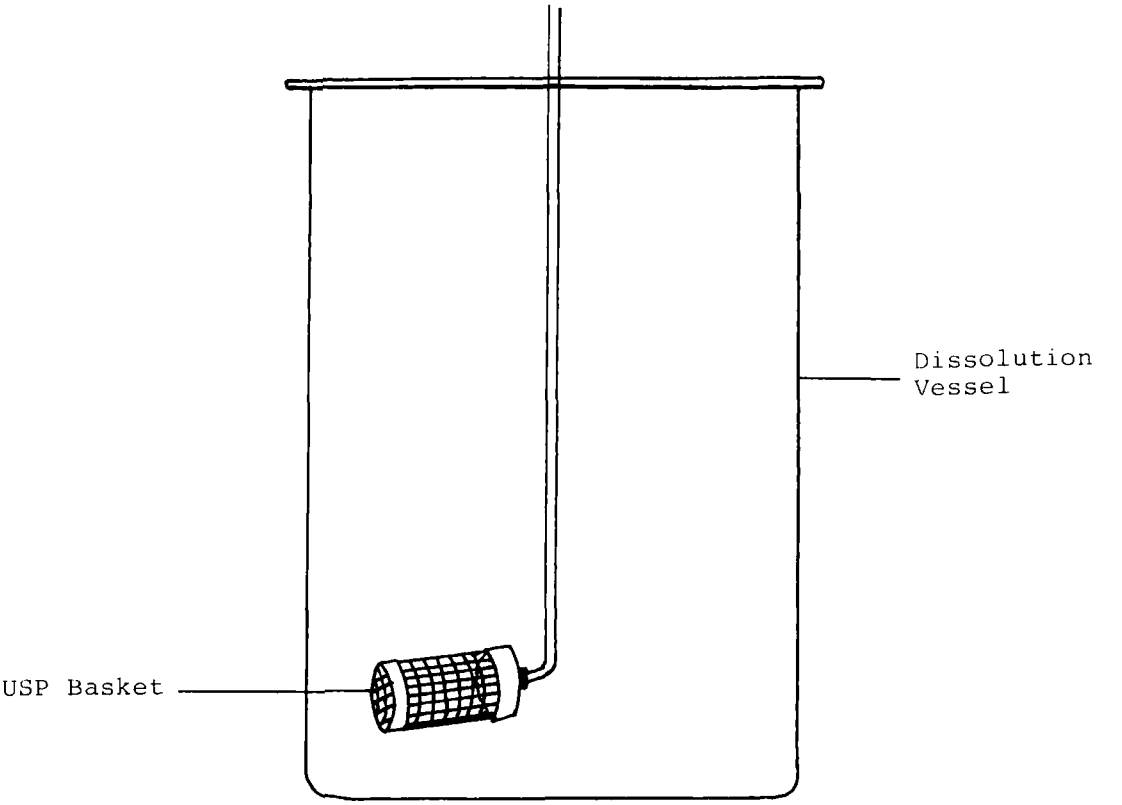

FIGURE 5 : Schematic Diagram of Modified USP Basket Apparatus.

that the tablet is held at a fixed distance from the center of rotation. Unquestionably, the increase in dissolution rate can be attributed to the greater flow of dissolution fluid over the tablet. The major disadvantage of this modified USP-NF basket or bent basket is the wandering of the dosage form within the basket at lower stirring speed of 60 r.p.m. However, inexpensive and simple construction of this device in addition to the dual functionality of the holder (i.e. holding the dosage form and stirring) are major advantages of this apparatus.

USP Paddle Method:

Another official method is the USP Paddle Method (30). The paddle methodology specifies that the paddle shaft be centered within 0.2 cm of the center line of the vessel. The shaft should rotate without discernible wobble and the bottom of the paddle should be 2.5 ± 0.2 cm from the bottom of the vessel (Fig. 6). There should be a minimal movement of the solid dosage form under the paddle until disintegration occurs. A cover plate with a center porthole and other holes is used. Shaft rotation is often maintained at 100 r.p.m. The temperature is maintained at 37 ± 0.5 °C. Aliquots should be drawn from the point that is midway between the upper edge of the paddle and surface of the medium and midway between the wall of the vessel and the stirrer shaft. The point of sampling changes if the volume of the dissolution medium in the vessel is decreased. The geometry of the container and shaft should be satisfying the compendial requirements. The paddle shaft should be vertically centered in the vessel which should, in turn, be on a horizontal plane. It is imperative to employ apparatus which avoids paddle wobble.

Ideally, the lower portion of each vessel should be hemispherical. Vessels should be uniform with respect to their weight, inside diameter and inside curvature. Statistically significant differences in dissolution rates have been reported when the same product was tested in different vessels.

The introduction of solid dosage units in the dissolution medium is staggered at one or two minute intervals. Thus, sufficient time is allowed for withdrawal of the aliquot, filtration, and the replacement of the fresh media. On the other hand, all

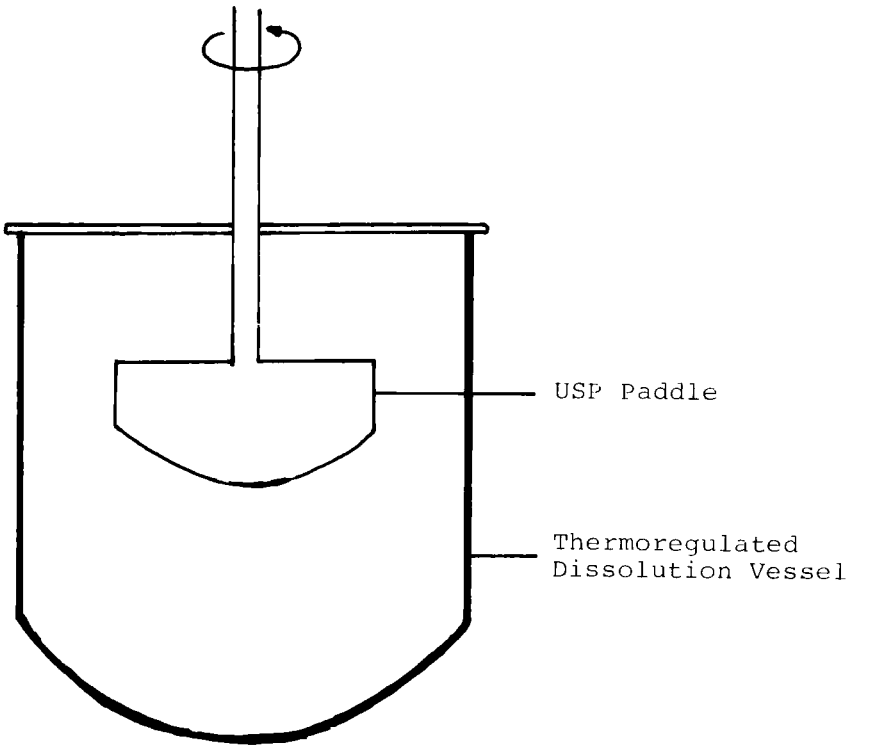

FIGURE 6 : Schematic Diagram of USP Paddle Apparatus.

the paddles must be introduced in the dissolution simultaneously. USP specifies the use of six apparatii at a time.

In this official method the sample container itself serves as a liquid stirring device. Under these conditions, there can be excessive abrasion and wear of the sample due to mechanical impacts with the container surface. This adversely affects its micro-environment. Although this assembly is simple in itself the aforementioned aspect should not be overlooked.

Rotating Filter-Stationary Basket:

The basic design of the Rotating Filter-Stationary Basket Apparatus includes a stationary sample basket, a large volume

fluid container and a rotating filter assembly with an external variable speed magnetic stirrer (34). The thermo-jacketted glass flask with a volume capacity of 1.5 liters of dissolution medium has a removable plexiglass cover. It has several ports, one port for the sample, one for the glass tube meant for the withdrawal of the aliquot from the rotating filter, another for the return of the dissolution fluid from the spectrophotometer flow cell and the fourth port for the thermometer.

The basket has a # 12 mesh screen in contrast to a # 40 mesh screen. It is kept stationary in contrast to the official method. The basket is held at the same position during each dissolution run due to the positioning by the plexiglass cover. The basket is held at 2 - 5 cm from the bottom of the flask.

The solid dosage form is introduced in the basket at the commencement of dissolution. This assembly is centered in the dissolution flask. The level of this assembly can be varied by changing the position of the glass tube. The assembly basically consist of a filter head, bottom flange, cylindrical filter due to flexible gasket, and a dynamic seal (Fig. 7).

The rotation of filter provides variable intensity of mild laminar liquid agitation. It permits continuous filtration of the samples of dissolution fluid and rotates at a fixed speed throughout the experiment.

The test is performed by suspending the solid dosage form in the basket an introducing it in the dissolution medium. Filtered fluid samples are continuously withdrawn through the glass tube at a flow rate of 40 ml/min for analysis.

A continuous flow system to maintain sink conditions has been reported for the Rotating Filter-Stationary Basket method (35).

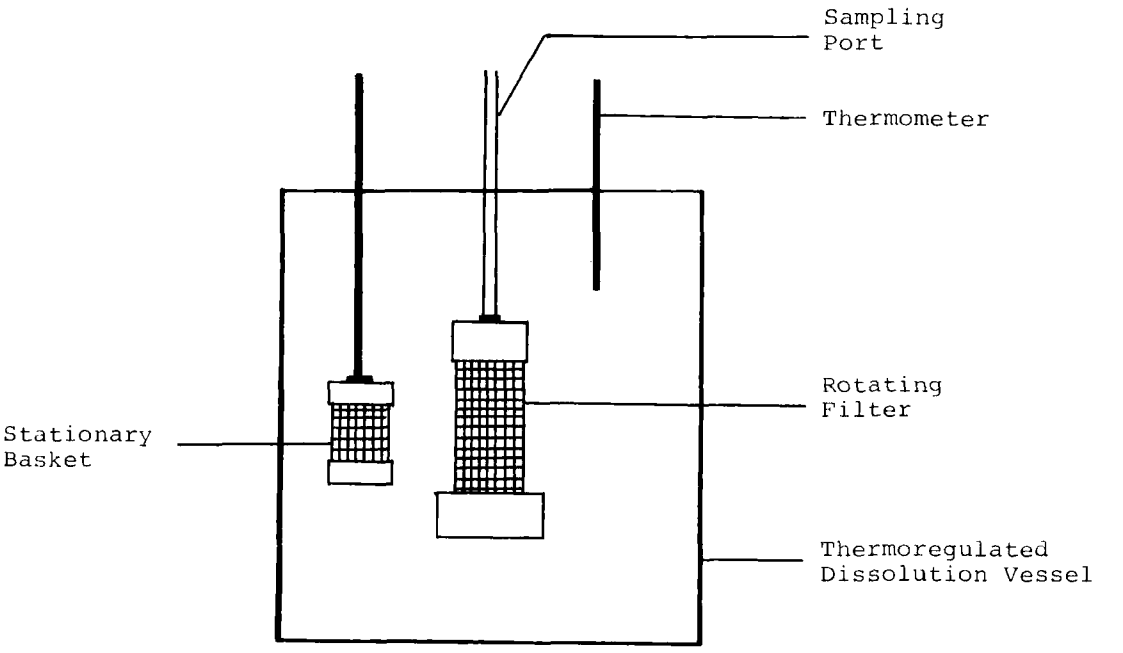

FIGURE 7 : Schematic Diagram of Rotating Filter-Stationary Basket Apparatus.

Powdered drugs are tested by dispersing a weighed amount of the sample in a small volume of dissolution medium and then it is transferred to the bulk medium. This assembly prevents excessive abrasion and wear of the sample due to mechanical impacts which is common to the official method.

This assembly serves as a liquid agitation device as well as an efficient fluid sampling system. The rotation of filter prevents plugging hydrodynamically. Its relatively mild agitation conditions, retainment of the microenvironment of the sample, and accurate positioning of the sample are added advantages.

Magnetic Basket Dissolution Apparatus:

Different dissolution rates from different dosage forms e.g. tablets and capsules of the same strength are a probability even when procuring (emanating) from the same manufacturer (36). A modified Levy Beaker Apparatus is constructed as shown if Fig. 8 (37, 38). It consists of a 800 ml beaker with an apparatus providing for reproducible and precise placement of the dosage form (tablet or capsule). Exact placement of the basket is ensured by attaching a magnetic bar to the outer bottom of the beaker and affixing a second magnet to the cylindrical basket. The second magnet, with attached basket, orients itself with exact reproducibility. The stainless steel wire basket is 50 mm long and has an inner diameter of 11 mm for capsules and 15 mm for tablets. An epoxy resin and hardener, inert in acidic and basic environment, is used in the construction of the magnetic basket. Each cylindrical basket is equipped with # 8 mesh hinged door openings at the ends of the cylinder. The dosage form under investigation is placed in the dry basket and the basket along with the magnetic assembly in the dissolution medium. The rate of stirring is electronically controlled at 60 r.p.m. by a constant speed, torque-controlled unit coupled to a servo motor generator. A three-bladed propeller, having a stirring diameter of 51 mm, with blades set at 60° angle to each other and 45° from vertical orientation, provides agitation. The blades have a diameter of 18 mm and are attached to a shaft 7 mm in diameter.

The dissolution containter containing 600 ml of dissolution medium is immersed in a constant-temperature jar at 37 ± 0.05° C and allowed to equilibrate. During each run the propeller is centered in the basket and immersed to a depth of 41 mm. Electrodes are

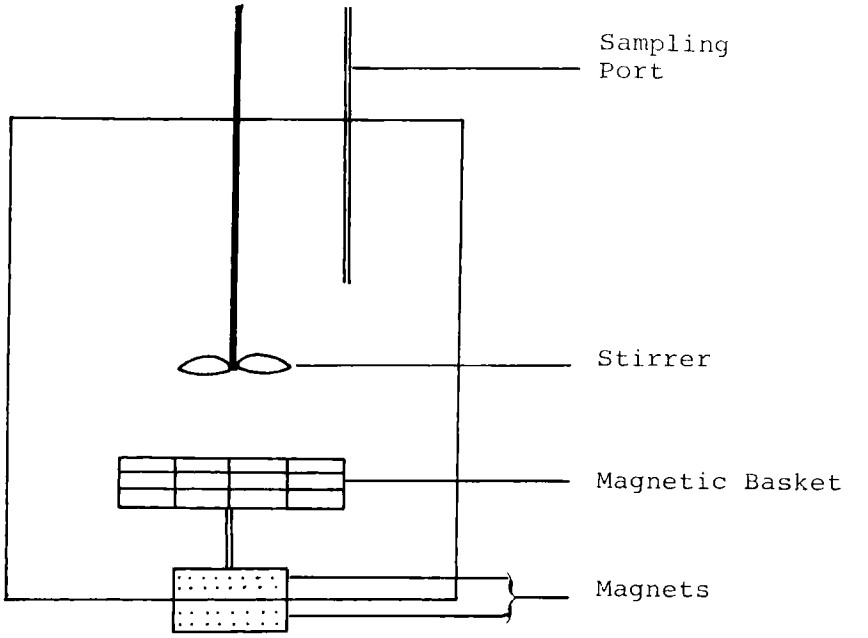

FIGURE 8 : Schematic Diagram of Magnetic Basket Dissolution Apparatus.

immersed to a depth of 27 mm and are 7 mm away from the wall of the beaker. On equilibration, the contents of the dissolution container adjusted to the required pH are introduced, following which the magnetic basket along with the dosage form to be examined is immersed.

The magnetic basket allows reproducible positioning of either a capsule or tablet in a hydrodynamic system such that the dissolution of the two different dosage forms can be studied employing the same parameters. This modification eliminates the possibility of "floating" capsules. However, the larger inner diameter of the basket does not give reproducible results for capsules, simply because they can assume more than one position within a larger

basket. This assembly lends itself to an automated analysis system as well as to manual sampling. With certain reservations, the system can be used to differentiate dissolution rates between products.

Continuous Flow Apparatii:

Several different types of dissolution containers, agitation methods, test media and sampling procedures have been used to determine dissolution profiles. However, most methodology is centered on USP Disintegration Apparatus or on the use of beaker stirrer assembly. It is now generally accepted that *in vitro* results should exhibit sufficient correlatibility to some physiological parameter. This can be possible if the dissolution system yields results which reflect physiological differences. Consequently, an apparatus whose operating characteristics can be easily changed should be designed. The development of an *in vitro* method which can serve to predict the rate of absorption of a specific drug would be the first step toward the development of *in vitro* methods for solid dosage forms. Keeping this in perspective, continuous flow apparatii for the determination of dissolution characteristics were designed.

A continuous fluid flow system provides a relatively simple and convenient test system applicable for the determination of dissolution rates of all drugs under sink conditions, regardless of their solubility and dosage strength. The sink conditions can be maintained by constant removal of the dissolved drug from the dissolution medium, facilitated by continuous elimination of the filtered dissolution medium from the dissolution chamber and simultaneous addition of fresh solvent in to the chamber. Continuous filtration of effluent dissolution medium isrformed by wire mesh

screen or other similar static filter elements. Filtration through such a static filter may not only introduce analytical errors in the dissolutation rate results due to the occurance of filter clogging, retarding fluid flow rates and escape of solid particles in to the filtrate. During the past several years, numerous continuous-flow methods, with or without cumulating reservoirs, have been reported (39-49). The contuous-flow apparatii described in the following sections are representative of the many, currently in operation.

a) Continuous Flow Apparatus by Pernarowski et al.:

A schematic diagram of Continuous Flow Apparatus employed by Pernarowski et al. (11), is illustrated in Fig. 9. The apparatus primarily constitutes a stainless steel basket stirrer assembly equipped with an adjustable stirrer. Ten-mesh stainless steel is used in the construction of th basket. This dissolution container is a one liter, three-necked flask. The main neck is 33 mm in diameter while the secondary necks are 20 mm in diameter. The total volume of the container is slightly greater than one liter.

If fluid flow or change over is necessary, the container is connected to a peristaltic pump. Flow rates up to 70 ml/min. can be used. Test fluids may be pumped directly to a collection container. Alternatively, they may be circulated through a 1 cm flow cell to the collection flask. Tubing lengths are kept to a minimum.

Dissolution characteristics may be determined by using exactly one liter of fluid or by operating the apparatus as a continuous flow system. If operated continuously, the volume of fluid in the dissolution container is slightly greater than one liter. Dissol-

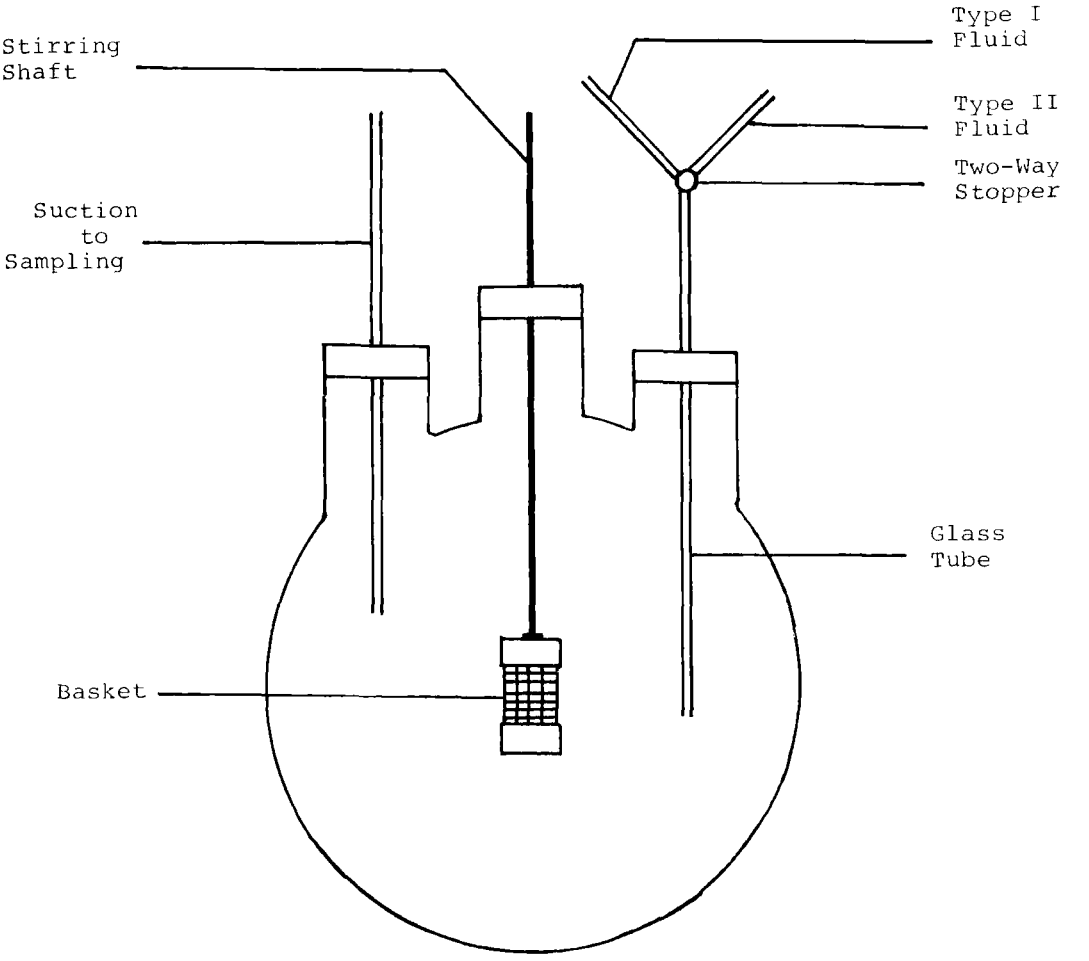

FIGURE 9 : Schematic Diagram of Continuous Flow Apparatus by Pernarowski et al.

ution characteristics are based on the amount of fluid pumped through the dissolution container.

This assembly can be easily automated but, at the same time, may be used as a simple flask-stirrer assembly with an auxillary system for media transfer. The operating characteristics can be easily altered. However, when conditions are fixed, similar

dissolution profiles are obtained when drug or tablets from a uniform lot are subjected to the procedure. Moreover, the basket stirrer assembly positions the tablet in the same way from run to run assisting in producing results characteristic of the product rather than of the apparatus.

b) Continuous Flow Apparatus by Baum and Walker:

Baum and Walker (12) designed an apparatus which they termed as constant circulation apparatus. The primary principle was that of Wiley Apparatus as reported by Meyers (50) with several modifications. Fig. 10 illustrates the principle components of the system. The apparatus consists of a glass dissolution cell in which the dosage form to be tested is placed, a reservoir for the dissolution medium, a continuous duty oscillating pump, and a suitable water bath in which the dissolution cell and reservoir are partially immersed. The rate of liquid flow through the cell is controlled by setting the variable transformer to a previously determined value. The lower screen of the dissolution cell is a # 100 mesh stainless steel screen, 1.8 cm in diameter.

The dissolution medium is poured into the reservoir and equilibrated at 37 ^{o}C. The pump is initially primed for higher flow rates facilitating residual air expulsion. A flow rate of 70 $\pm$ 2 ml/min. is found to be satisfactory. The tablet is dropped into the dissolution cell and the upper screen is inserted on commencement of the dissolution test.

This constant circulation apparatus lends itself for modification as regards to dissolution chamber and size of chamber if deemed necessary for different size dosage forms. The use of any size reservoir makes it possible to achieve solutions of any

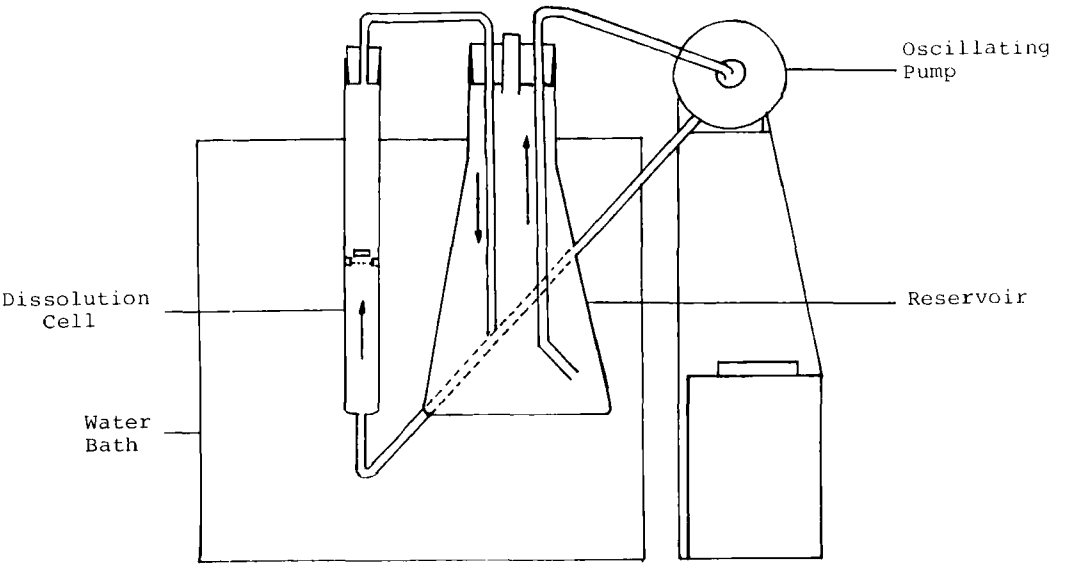

FIGURE 10 : Schematic Diagram of Continuous Flow Apparatus by Baum and Walker.

degree of saturation facilitating evaluation of pharmaceutical formulations, particularly in the correlation with *in vivo* results and the "perfect sink" conditions presented in the literature. Agitation would be provided by suitable stirring mechanism. For the most part, tablets remain below the screen, however, depending on density, tapped air, etc., may rise and rule against the screen, thus influencing dissolution.

The test fluid may be introduced through the top screen, but no data have been presented with reverse flow which would be useful with certain lower density type dosage forms. The introduction of an opposing stream of dissolution medium from the top of the chamber with a suitable chamber design, might provide a suspended system. It is needless to say the specificatons could vary, but should be

standardized in the light of reproducibility, laminar and turbulent flow.

c) Continuous Flow Apparatus by Tingstad and Riegelman:

The apparatus consists of a cylindrical glass dissolution cell, 6.1 cm long and 1.9 cm in diameter, constructed from two small-volume glass filter funnels (13). A schematic diagram of the assembly is illustrated in Fig. 11. The dissolution cell facilitates the use of filter membranes of sufficient retentive characteristics which prevent solid particles from reaching the analyzer. The solvent flow to the system is controlled by external valves, with the excess capacity of the pump being recirculated to the reservoir. The air trap prevents air bubbles from distorting the analytical reading.

The assembly is submerged in a constant-temperature bath, including the flowmeter, lower filter, dissolution cell, and lower part of the upper filter piece/air trap. On equilibration, the pump is turned on and the flow is regulated to the desired flow rate. The air outlet, open when the pump is turned on, is closed to the analyzer as soon as the liquid level in the air trap is above the outlet tube.

It should be emphasized that the described apparatus is a prototype, and numerous improvements are both possible and probable as more experience is gained. The cross-sectional flow or solvent flow is a variable that must be taken into account. Volume of the dissolution cell should be minimized to optimize homogenity of the system. In addition, the size and shape of the air trap should be altered to optimize shape and minimum size, as any mixing and pooling of solution beyond the dissolution cell tend to distort the analytical tracing. The system should lend itself easily to automation.

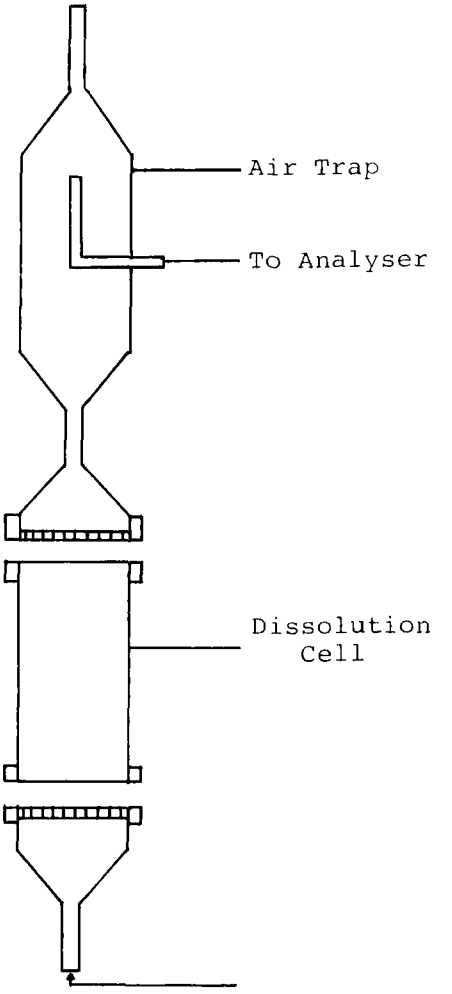

FIGURE 11 : Schematic Diagram of Continuous Flow Apparatus by Tingstad and Riegelman.

There is little doubt that, based on theoretical considerations, this method is superior to present methods both for the fundamental and practical studies. It possibly has the inherent flexibility that may allow it to meet, with the appropriate modification, most or all of the requirements listed for the ideal dissolution rate method.

d) Multi-chamber Continuous Flow Apparatus by Cakiryildiz et al.:

The dissolution system consists of a six channel peristaltic pump, a thermostated water bath with a magnetic stirring plate for six beakers, an additional smaller water bath, an analyser equipped with an automated cell changer and recorder, and five identical independent dissolution units with a sixth for recirculation of a reference solution (51). From the reservoir, the dissolution medium goes (via the pump) to the flow-through quartz cell, to the bottom of the dissolution cell, and from its top, returns to the reservoir.

The dosage form under investigation is placed on top of a bed of glass beads (0.2 mm, 20 g) in the dissolution cell and the cell is closed. One liter of simulated gastric fluid USP (without pepsin) is used for drug powders. Less liquid is employed for capsules and tablets so that maximum concentration of drug in solution does not exceed 10-15% of its saturation solubility. A flow rate of 8.0 ± 0.2 ml/min. is used for drug powder and the same or 16 ± 0.5 ml/min. is employed for capsule dissolution studies. These rates minimize pressure buildup at the membrane filter. A flow rate of 33 ± 1. ml/min. is maintained for tablet dissolution studies.

The apparatus, as described, lends itself to mechanical abrasion (scratching) by glass beads. A more serious drawback is the low recovery observed in powder studies due to retention of undissolved drug in scratches on the inner wall of the cell. However, the apparatus is versatile enough to determine dissolution patterns of drug powders and of tablet and capsule formulations with any change of the experimental setup. In addition to being capable of showing formulation differences, the apparatus is sensitive enough to reveal process changes (51).

Pressure Controlled Apparatus:

A special modification of the USP Basket Method led to the development of an apparatus employing pressurized air for the purpose of agitation. The design of this apparatus (Fig. 12) consists of two tubes, one tube being 28.4 cm x 3.4 cm i.d. and the other is 29.4 cm x 2.8 cm i.d., connected in turn by two tubes each of 4.7 cm x 1.0 cm i.d. (52). Air at pressures of 40, 43, 46, 50, and 55 mm of mercury is used to provide agitation to the dissolution medium. The basket is positioned 15.7 cm away from the bottom of the tube with larger diameter. Air bubbles are avoided by the use of a venting tube at the top of this tube. The cylindrical basket is made of stainless # 40 mesh wire cloth, 3.66 cm high and 2.5 cm in diameter. The basket consists of a solid metal top with a small vent. The basket, loaded with the dosage form to be tested, is suspended in the tube with the larger diameter.

At the bottom of the tube with the larger diameter, is a porcelain stone projecting through the circular hole in the center. The stone is encircled by a # 40 mesh stainless steel screen inside a rubber supported by a stainless sleeve. An opening at the bottom of the porcelain stone is connected by a 5.5 mm polythene tubing to an air pump through a mercury manometer.

The temperature of the dissolution medium is maintained at 37 °C and the dosage form within the basket is suspended in the media. Air flow is controlled by a pump attached with a mercury manometer. The circulation of the dissolution medium is maintained by air pressure. The aliquots are withdrawn from tubes with smaller diameter.

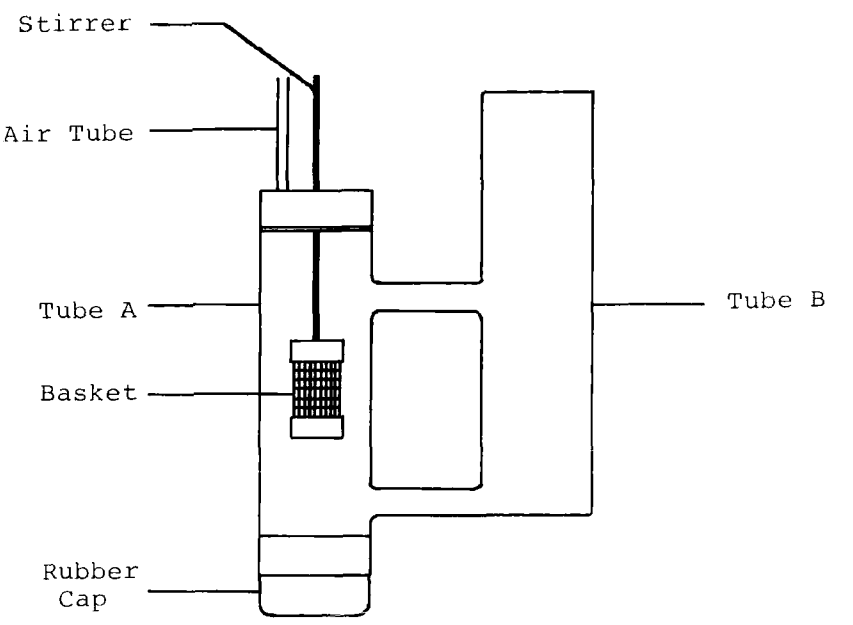

FIGURE 12 : Schematic Diagram of Pressure Controlled Dissolution Apparatus by Nasir et al.

This method uses air pressure for agitation in contrast to the official method where the medium is de-aerated to avoid air bubbles. This dissolution apparatus is reported to have yielded results comparable with the Levy Method at an air pressure of 46 mm of mercury. No excessive settling of particles and no clogging of screen is observed in addition to complete dissolution of the dosage form under investigation. Poor agreement was observed in the dissolution rates of the drugs tested in USP Dissolution Apparatus as compared to the new apparatus at all pressures. The possibility exists, however, that tablets with significantly different properties may produce contrary results.

DISCUSSION:

It has now been recognized beyond doubt that the dissolution rate of a drug from its dosage form can become the rate-limiting process in the physiological availability and in vivo absorption of the drug. Interest has been focused on designing an in vitro dissolution test model that can positively characterize the role of the dissolution process in drug bioavailability. Such an apparatus should meet the following criteria:

1. The fabrication, dimensions and positioniong of each individual component must be precisely specified.
2. Simplicity of design, convenience of operation and flexibility in use under a variety of test conditions must be the over-riding considerations.
3. The apparatus should be sensitive enough to reveal process changes and capable of showing formulation differences. However, it should yield reproducible results upon repeated testing under identical conditions.
4. The apparatus should permit controlled variable intensity of mild, uniform, non-turbulent liquid agitation.
5. The apparatus should provide and maintain nearly perfect sink conditions during in vitro dissolution rate determinations; i.e. the drug concentration in the dissolution medium should not exceed 10-20% of its solubility.
6. The apparatus must provide a convenient means for introducing the dosage form under investigation (tablet, capsule, etc.) in to the dissolution medium, in addition to holding it at a fixed position completely immersed in the medium.

7. The test sample must be subjected to minimal mechanical impacts, abrasion and wear during the entire test period in order to retain its microenvironment.
8. The dissolution medium container must be closed to prevent loss of medium due to evaporation, thermo-regulated at fixed temperature, and preferably transparent to permit visual observation.
9. The apparatus must lend itself to easy withdrawal of representative fluid samples of the bulk medium for analysis, either by manual or automated methods without interrupting medium agitation. An automated system should permit continuous filtration efficiently without encountering operational and/or analytical difficulties.
10. The apparatus must be applicable for the evaluation of disintegrating, non-disintegrating, dense or "floating" tablets and capsules, finely powdered drugs, and all other types of solid drug forms.
11. The apparatus should be rugged enough so that critical parameters result in good inter-laboratory agreement.

The recent sharp increase in the amount of dissolution esting carried out by the pharmaceutical industry reflects growing recognition of the technique's value. Dissolution tests are critical and difficult to carry out properly. If one is to obtain correct results, care and attention must be given to those aspects that have been identified as crucial.

Present methods suffer from the disadvantage as to their empirical nature of stirring or rocking as a device for ensuring homogenity and moving solvent/solute molecules. Due to this empirical

nature, they cannot be related to fundamental dissolution rate equations except by including them in a catch-all constant, which is a very superficial solution to the problem. As a result, it is crucial that the various test systems be standardized as much as possible: one stirring rate, one type of container, one type of solvent, etc. But this greatly reduces investigative flexibility which is a primary requisite for a good standard method. Furthermore, with such rigid constraints, the procedures will be less quantitative and less meaningful.

CONCLUSIONS:

For obvious reasons, it would be ideal if one relatively simple and inexpensive apparatus and method could be used to determine the dissolution rates of most drugs and drug products. However, standing in the way of a one-method concept is the fact that a great variety of factors influence the results obtained from dissolution rate tests.

Controversy still exists as to the usefulness and validity of the *in vitro* dissolution method as far as correlation with *in vivo* results is concerned. The development of an *in vitro* method which can serve to predict the *in vivo* performance of a specific drug would be the first step towards developing and designing of dissolution systems. Unquestionably, poor *in vitro/in vivo* correlations may in some instances reflect the variability of the *in vitro* dissolution procedure employed, as well as inter and intra-subject variation *in vivo*. No universal dissolution test method has yet been devised that in every instance gives the same rank order for *in vitro* dissolution and *in vivo* availability for different formulations or batches (53).

There is presently an acknowledged scarcity of data showing correlation between in vitro/in vivo performance of drugs and drug products. However, the great current interest and activity in this area indicate that more and more data is forthcoming. With the increase in accumulation of knowledge in this area, difficulties, problems, and deficiencies in the in vitro methods will be exposed, necessitating refinement in equipment and procedures. The more flexible the standard method is, the more easily it will lend itself to modifications warranted by new findings.

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